

Thermodynamic Study of the Solubility of Benzoin in Ethyl Acetate (1)+ Ethanol (2) Mixtures

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Abstract: The equilibrium solubilities of benzoin (3) in ethyl acetate+ethanol mixtures were determined at several temperatures from 283.15-323.15 K. The Gibbs energy, enthalpy and entropy of solution and of mixing were obtained from these solubility data. The solubility was maximal in the mixture with $w_1 = 0.90$ and very low in pure ethanol at all the temperatures studied. A non-linear plot of $\Delta_{\text{soln}}H^\circ$ vs. $\Delta_{\text{soln}}G^\circ$ with negative slope from pure ethanol up to 0.1 in mass fraction of ethanol and positive beyond this composition up pure ethyl acetate was obtained at the mean temperature, 302.6 K. Accordingly, the driving mechanism for benzoin solubility in the ethanol-rich mixtures was the entropy and for the ethyl acetate-rich mixtures it was the enthalpy.

Key words: Benzoin, solubility, {ethyl acetate+water} mixtures, Jouyban-Acree Model, thermodynamic quantities, entropy

INTRODUCTION

Benzoin (2-hydroxy-1, 2-diphenylethan-1-one), CAS No. 119-53-9, $C_{14}H_{12}O_2$, molar mass: 212.24 g/mol, molecular structure shown in Fig. 1 benzoin is used to synthesize drugs like oxaprozin an nonsteroidal anti-inflammatory drug, ditazole which is a platelet aggregation inhibitor and Fenhytoin is an anti-seizure medication (Yang *et al.*, 2017a, b; Carl and Smith, 1992; Mahmoodi and Emadi, 2004). At present, studies of solubility and thermodynamic analysis of drugs in organic solvents have taken on relevance. These data are of great importance for the approach of strategies for the development of different processes that go from the formulation of medicines, purification of chemically active

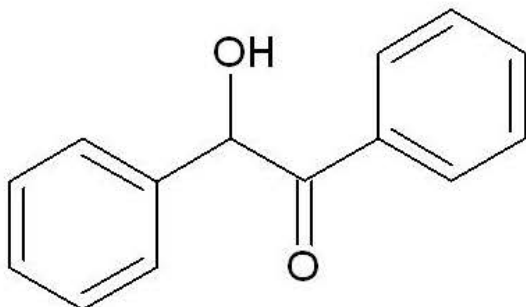


Fig. 1: Molecular structure of benzoin

substances, environmental treatments and the design of more efficient industrial processes (Carvajal *et al.*, 2016; Serrezuela *et al.*, 2017a-c; Letcher, 2007).

Regarding the drug solubility studies, despite they are of great importance in the pharmaceutical industry, at present, they have also taken relevance in environmental studies because of the risk represented by antibiotics for microbial flora of aquatic ecosystems (Serrezuela *et al.*, 2017a-c; Letcher, 2007). In this context and according to what was stated in the previous paragraph, due to the increase of commercial products containing benzoin, several researchers have started to develop techniques to eliminate this drug from environmental systems (Ueyama *et al.*, 1991).

For these reasons, the main goals of this research are to extend the database on experimental solubility for benzoin and also, to evaluate the effect of the cosolvent composition on solubility and dissolution thermodynamics of benzoin in binary mixtures conformed by ethyl acetate and ethanol. This is based on the van't Hoff method, including the respective contributions by the mixing of this compound toward the dissolution processes as has been made with some other drugs in the same mixtures (Serrezuela *et al.*, 2018a, b; Serrezuela and Chavarro, 2016 Ruidiaz *et al.*, 2010; Benavides *et al.*, 2018) and other common cosolvent systems (Cardenas *et al.*, 2015; Montiel *et al.*, 2017; Serrezuela *et al.*, 2016a, b; Cristancho *et al.*, 2016). In this way, this research

expands the solubility values presented in our previous communication (Serrezuela *et al.*, 2016a, b). As well known aqueous cosolvent mixtures are the best solubilizing technique in pharmaceutical and chemical sciences (Jouyban, 2009; Losada *et al.*, 2018).

MATERIALS AND METHODS

Reagents: In this research, benzoin (Sigma-Aldrich, USA; compound 3; with purity of at least 0.990 in mass fraction), ethyl acetate (Merck A.R., Germany; the solvent component 1, purity at least 0.998 in mass fraction) and ethanol (Merck A.R., Germany; the solvent component 2, purity at least 0.998 in mass fraction) were used.

Calorimetric study: Melting behavior of benzoin as original sample and bottom solid phase at equilibrium with saturated solutions in neat ethanol, neat ethyl acetate and the mixture $w_1 = 0.50$ were determined by Differential Scanning Calorimetry (DSC) studies (TA Instruments DSC 2920, USA). Thermal analyses were performed at a heating rate of 10 K/min in a dynamic nitrogen atmosphere (10 cm³/min). Nearly 5.0 mg of benzoin was analyzed in each case. The equipment was calibrated using indium as standard. General procedures was similar to those used before with different drugs in {ethyl acetate (1)+ethanol (2)} mixtures (Delgado *et al.*, 2016; Serrezuela *et al.*, 2018a, b; Cardenas *et al.*, 2017; Perdomo *et al.*, 2017).

RESULTS AND DISCUSSION

The solubility of benzoin in ethyl acetate and ethanol mixtures (Fig. 2) was taken from the literature (Yang *et al.*, 2017a, b).

Equilibrium solubility of benzoin: Table 1 reports the experimental solubility of the benzoin expressed in mole fraction at 283.15, 288.15, 293.15, 298.15, 303.15, 308.15, 313.15, 318.15 or 323.15 K (± 0.05 K). Figure 2 shows the solubility profiles, as a function of the polarity of the mixtures, expressed by their solubility parameters (δ_{mix}). For a binary mixture δ_{mix} can be calculated from the solubility parameter of the pure solvents ($\delta = 18.1$ MPa^{1/2} for ethyl acetate and $\delta = 26.5$ MPa^{1/2} for ethanol (Serrezuela *et al.*, 2017a-c) and the volume fraction ϕ_i of each component in the mixture which is calculated assuming additive volumes (Connors, 2002):

$$\delta_{mix} = \delta_1\phi_1 + \delta_2\phi_2 \quad (1)$$

The solubility increases with temperature in all cases indicating that the dissolution process is endothermic. Considering the entire polarity region, the solubility increase from pure ethanol ($\delta = 26.5$ MPa^{1/2}) up to the mixture with $w_1 = 0.90$ ($\delta_{mix} = 18.9$ MPa^{1/2}) where the curve shows a maximum solubility peak, from this mixture up to pure ethyl acetate the solubility decrease in all cases. This behavior is unusual, since, in theory, benzoin should be

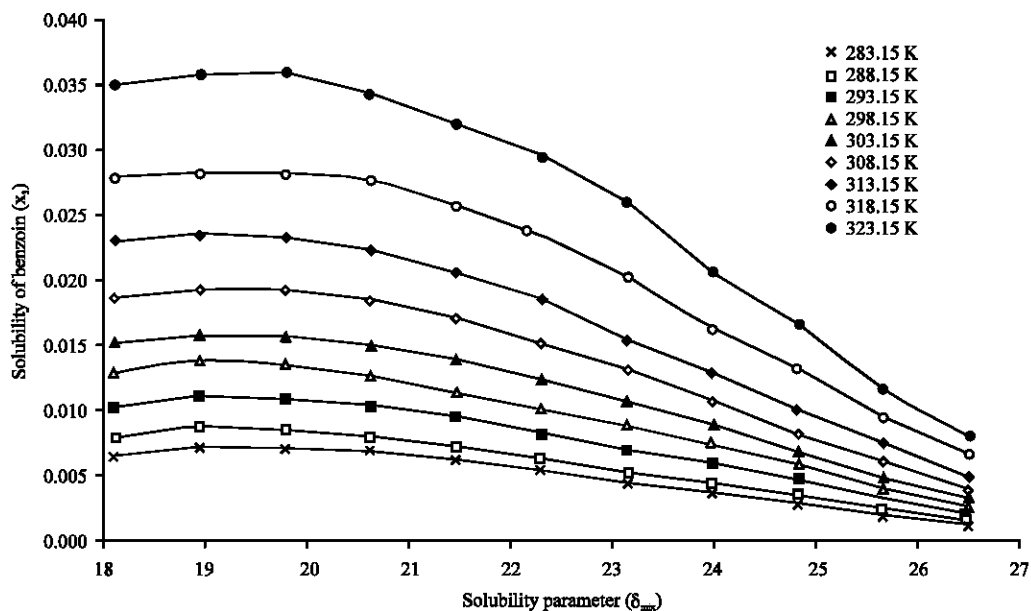


Fig. 2: Experimental mole fraction solubility of benzoin (3) against the solubility parameter of the {ethyl acetate (1) + ethanol (2)} mixtures (δ_{mix})

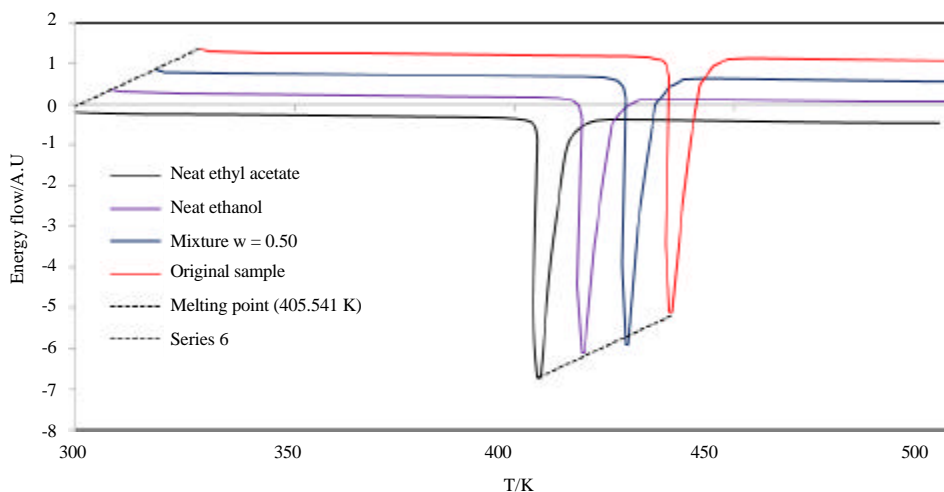


Fig. 3: DSC thermograms of the solid phases in equilibria with the saturated solutions. From top to bottom: neat dioxane, mixture $w_1^\circ = 0.50$, neat water and original sample

Table 1: Experimental and ideal solubility of benzoin (3) (x_3) in {ethyl acetate (1)+ethanol (2)} mixtures expressed as mole fraction at several temperatures

δ_1^a	283.15 K	288.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K	323.15 K
26.5	1.14×10^{-3}	1.47×10^{-3}	2.00×10^{-3}	2.50×10^{-3}	3.22×10^{-3}	3.87×10^{-3}	4.92×10^{-3}	6.57×10^{-3}	7.95×10^{-3}
25.7	1.94×10^{-3}	2.46×10^{-3}	3.19×10^{-3}	3.98×10^{-3}	4.76×10^{-3}	6.07×10^{-3}	7.50×10^{-3}	9.53×10^{-3}	1.16×10^{-2}
24.8	2.82×10^{-3}	3.40×10^{-3}	4.64×10^{-3}	5.86×10^{-3}	6.74×10^{-3}	8.13×10^{-3}	1.01×10^{-2}	1.32×10^{-2}	1.65×10^{-2}
24.0	3.64×10^{-3}	4.36×10^{-3}	5.92×10^{-3}	7.35×10^{-3}	8.93×10^{-3}	1.07×10^{-2}	1.29×10^{-2}	1.63×10^{-2}	2.06×10^{-2}
23.1	4.41×10^{-3}	5.21×10^{-3}	6.96×10^{-3}	8.75×10^{-3}	1.06×10^{-2}	1.31×10^{-2}	1.54×10^{-2}	2.02×10^{-2}	2.59×10^{-2}
22.3	5.31×10^{-3}	6.24×10^{-3}	8.29×10^{-3}	1.00×10^{-2}	1.23×10^{-2}	1.50×10^{-2}	1.85×10^{-2}	2.34×10^{-2}	2.94×10^{-2}
21.5	6.16×10^{-3}	7.20×10^{-3}	9.47×10^{-3}	1.13×10^{-2}	1.38×10^{-2}	1.71×10^{-2}	2.06×10^{-2}	2.57×10^{-2}	3.19×10^{-2}
20.6	6.82×10^{-3}	7.94×10^{-3}	1.04×10^{-2}	1.26×10^{-2}	1.49×10^{-2}	1.84×10^{-2}	2.23×10^{-2}	2.76×10^{-2}	3.42×10^{-2}
19.8	7.07×10^{-3}	8.43×10^{-3}	1.09×10^{-2}	1.35×10^{-2}	1.56×10^{-2}	1.92×10^{-2}	2.32×10^{-2}	2.82×10^{-2}	3.57×10^{-2}
18.9	7.16×10^{-3}	8.73×10^{-3}	1.11×10^{-2}	1.38×10^{-2}	1.57×10^{-2}	1.92×10^{-2}	2.35×10^{-2}	2.82×10^{-2}	3.57×10^{-2}
18.1	6.48×10^{-3}	7.86×10^{-3}	1.02×10^{-2}	1.29×10^{-2}	1.51×10^{-2}	1.86×10^{-2}	2.30×10^{-2}	2.78×10^{-2}	3.50×10^{-2}
Ideal	2.13×10^{-2}	2.57×10^{-2}	3.09×10^{-2}	3.70×10^{-2}	4.43×10^{-2}	5.27×10^{-2}	6.27×10^{-2}	7.43×10^{-2}	8.78×10^{-2}

^a δ_1 is the parameter solubility of {Ethyl acetate (1)+ethanol (2)} mixtures free of benzoin (3)

much more soluble in ethanol because the polarity of this solvent is similar to that of the solute. Thus, although, benzoin is much more polar than ethyl acetate, so, it should be less soluble in this solvent, this could be due to the steric effect of the two rings of the molecule which would limit the molecular interactions between the benzoin and ethanol and would favor the molecular interactions between benzoin and ethyl acetate ($\delta_1 < \delta_3 \approx \delta_2$ or $\delta_2 \approx \delta_3 > \delta_1$).

According to the literature, solutes reach their maximum solubility in solvents with the same solubility parameter (Trujillo *et al.*, 2018) and thus, the δ value of benzoin (3) would be $26.53 \text{ MPa}^{1/2}$. It is noteworthy that this is a special case. The solute is more soluble in a mixture whose polarity is very different and poorly soluble in the solvent (ethanol) whose polarity is similar. Nevertheless, the solubility parameter of benzoin (3), estimated according to the group contribution methods proposed by Fedors and van Krevelen is $\delta = 26.53 \text{ MPa}^{1/2}$ (Delgado *et al.*, 2012) which is greater than

the experimental value obtained in this work at the solubility maximum ($\delta = 18.9 \text{ MPa}^{1/2}$). This behavior was also observed previously with several other drugs (Sanchez *et al.*, 2018). This fact could indicate that the actual polarity of benzoin is lower than the one expected from the additive contribution of its groups. As was indicated earlier, it is well known that the group contribution methods only provide a rough estimation of δ , however, this calculation is very useful to approximate the solvent or the most suitable solvent mixture for dissolving the drug. Therefore, these calculations have great advantages in experimental and industrial designs (Pena *et al.*, 2009).

Figure 3 depicts the thermal behavior of the solid phases involved in equilibrium with the saturated solutions in neat ethyl acetate, neat ethanol and the mixture $w_1^\circ = 0.50$ as well as the original untreated drug sample. As observed, in all cases a mean fusion peak of benzoin is observed near to 405.541 K which is coincident with the melting point reported by Yang *et al.* (2017a, b).

Table 2: Benzoin (3) activity coefficients (3) in {Ethyl acetate (1)+ethanol (2)} mixtures at several temperatures

w ₁ ^a	283.15 K	288.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K	323.15 K
0.00	18.69	17.48	15.45	14.82	13.75	13.63	12.74	11.30	11.04
0.10	10.98	10.45	9.69	9.31	9.30	8.69	8.36	7.79	7.55
0.20	7.56	7.56	6.66	6.32	6.57	6.49	6.22	5.64	5.31
0.30	5.85	5.89	5.22	5.04	4.96	4.93	4.87	4.56	4.26
0.40	4.83	4.93	4.44	4.23	4.18	4.02	4.07	3.68	3.39
0.50	4.01	4.12	3.73	3.69	3.59	3.51	3.39	3.18	2.98
0.60	3.46	3.57	3.26	3.27	3.20	3.09	3.05	2.89	2.75
0.70	3.12	3.24	2.97	2.94	2.96	2.86	2.81	2.69	2.57
0.80	3.01	3.05	2.83	2.75	2.83	2.75	2.70	2.64	2.46
0.90	2.98	2.94	2.80	2.68	2.82	2.75	2.67	2.63	2.46
1.00	3.29	3.27	3.03	2.88	2.93	2.84	2.72	2.67	2.51

^aw₁^o is the mass fraction of ethyl acetate (1) in the {ethyl acetate (1)+ethanol (2)} mixtures free of benzoin (3)

(Serrezuela *et al.*, 2018a, b). In this way, it is possible to establish that the solid phases in equilibrium with the saturated solutions in water and water-rich mixtures are the same as the original sample.

Activity coefficients of benzoin: Table 2 gives the activity coefficients of benzoin (3) δ_3 , at all temperatures and mixture compositions which were calculated as the quotient $x_{id,3}/x_3$ from the respective mole fraction solubility values presented in Table 1. The calculated activity coefficients allow one to obtain a rough estimate of solute-solvent intermolecular interactions through Eq. 2 (Kristl and Vesnaver, 1995):

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{12}) \frac{V_3 \phi_1^2}{RT} \quad (2)$$

Here subscript 1 stands for the solvent systems (which in the present case is the {ethyl acetate (1)+ethanol (2)} solvent mixture) or the neat solvents ethyl acetate and water. Further, e_{11} , e_{33} and e_{13} represent the solvent-solvent, solute-solute and solvent-solute interaction energies, respectively, V_3 is the molar volume of the super-cooled liquid drug solute and ϕ_1 is the volume fraction of the solvent mixture. Since, the solubility of benzoin is very low, more in particular in water-rich mixtures, the volume fraction of the solvent is nearly unity and the $(V_3 \phi_1^2 / RT)$ term can be considered a constant at the given temperature. Thus, the activity coefficients depends mainly of the respective molecular interactions (e) (Kristl and Vesnaver, 1995). The e_{11} and e_{33} terms are unfavorable for the dissolution processes whereas the e_{13} term favors these processes. Generally, the contribution from the e_{33} term is considered as constant in all mixtures containing the dissolved solute. The term e_{33} represents solute-solute interactions which to a first approximation would be the same irrespective of the properties of the dissolving solvent media. Performing an analysis based on the on the magnitudes of the energetic quantities in Eq. 2, it is inferred that the term e_{11}

term is the highest in pure ethanol (2) (Hildebrand solubility parameter $\delta = 26.5 \text{ MPa}^{1/2}$) and is smallest in ethyl acetate-rich mixtures.

The values of the activity coefficients increase from pure ethanol up to the mixture with $\delta_{\text{mix}} = 18.9 \text{ MPa}^{1/2}$, indicating a possible increase in solute-solvent interactions which favors the increase in solubility. From this mixture, a sharp increase in the activity coefficient is observed again, so, it is assumed that the solute-solute and solvent-solvent interactions increase, decreasing the solubility of benzoin (3). In all cases, γ_3 values decrease with the temperature increasing. It is conjecturable to assume that the highest solvation of benzoin (3) is observable in ethyl acetate-rich mixtures.

Apparent thermodynamic quantities of benzoin (3)

dissolution: From solubility data, the thermodynamic functions of dissolution are calculated. So, the apparent standard molar enthalpy change of dissolution, $\Delta_{\text{soln}}H^\circ$ is obtained from the slope of a $\ln x_3$ vs. $1/T - 1/T_{\text{hm}}$ plot. Over the limited temperature interval (298.15-313.15 K) the heat capacity change of solution may be assumed to be constant, hence, $\Delta_{\text{soln}}H^\circ$ should be valid for the mean harmonic temperature, $T_{\text{hm}} = 303.0 \text{ K}$ (Pedraza *et al.*, 2018):

$$\Delta_{\text{soln}}H^\circ = -R \left(\frac{\partial \ln x_3}{\partial \left(\frac{1}{T} - \frac{1}{T_{\text{hm}}} \right)} \right)_p \quad (3)$$

The apparent standard Gibbs energy change for the dissolution process ($\Delta_{\text{soln}}G^\circ$), considering the approach proposed by Krug *et al.* (1976) is calculated at 303.0 K by means by Pedraza *et al.* (2018):

$$\Delta_{\text{soln}}G^\circ = -RT_{\text{hm}} \cdot \text{intercept} \quad (4)$$

The standard molar entropy change for the solution process, $\Delta_{\text{soln}}S^\circ$, at the mean harmonic Temperature, $T_{\text{hm}} = 302.5 \text{ K}$ is then obtainable by means of:

Table 3: Apparent thermodynamic functions relative to dissolution processes of benzoin (3) in {ethyl acetate (1) + ethanol (2)} mixtures at $T_{hm} = 303.0$ K

w_1°	$\Delta_{soln}G^{\circ}/\text{kJ}\cdot\text{mol}^{-1}$	$\Delta_{soln}H^{\circ}/\text{kJ}\cdot\text{mol}^{-1}$	$\Delta_{soln}S^{\circ}/\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$	$T\Delta_{soln}S^{\circ}/\text{kJ}\cdot\text{mol}^{-1}$	ζ_H	ζ_{TS}
0.00	14.53	36.79	73.58	22.26	0.62	0.38
0.10	13.41	33.88	67.63	20.47	0.62	0.38
0.20	12.55	33.01	67.58	20.45	0.62	0.38
0.30	11.94	32.51	67.98	20.57	0.61	0.39
0.40	11.46	33.32	72.22	21.86	0.60	0.40
0.50	11.06	32.49	70.81	21.43	0.60	0.40
0.60	10.76	31.32	67.94	20.56	0.60	0.40
0.70	10.55	30.64	66.40	20.09	0.60	0.40
0.80	10.44	30.34	65.79	19.91	0.60	0.40
0.90	10.41	29.87	64.33	19.47	0.61	0.39
1.00	10.54	31.79	70.22	21.25	0.60	0.40
Ideal	7.87	26.93	62.98	19.06	0.59	0.41

w_1° is the mass fraction of ethyl acetate (1) in the {Ethyl acetate (1)+ethanol (2)} mixtures free of benzoin (3)

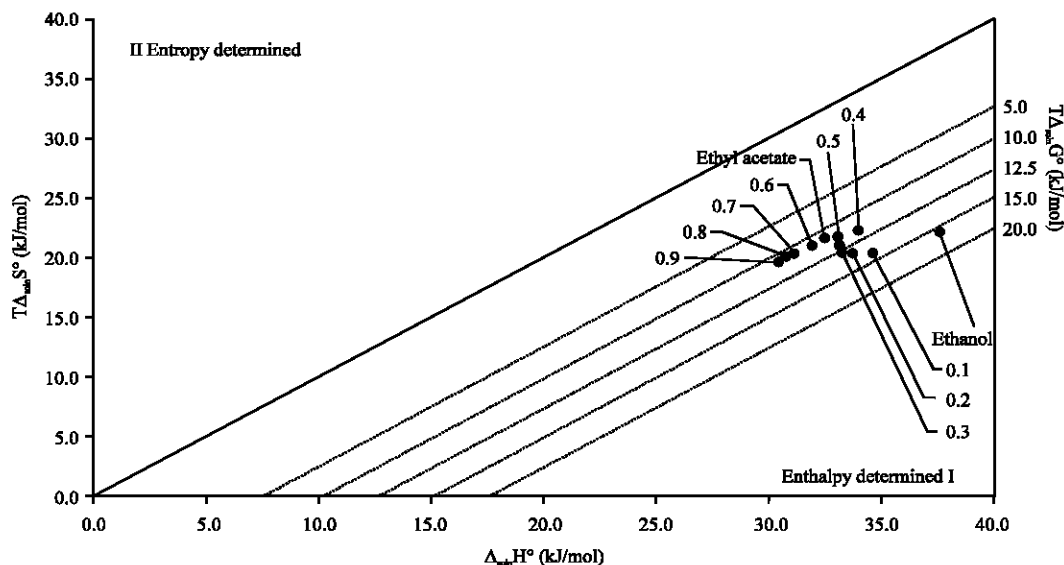


Fig. 4: Relationship between the enthalpy and entropic terms of solutions functions of benzoin (3) in {ethyl acetate (1)+ethanol (2)} mixtures at $T_{hm} = 303.0$ K. The isoenergetic curves of $\Delta_{soln}G^{\circ}$ function are marked by dotted lines

$$\Delta_{soln}S^{\circ} = \frac{\Delta_{soln}H^{\circ} - \Delta_{soln}G^{\circ}}{T_{hm}} \quad (5)$$

Table 3 presents the standard molar thermodynamic functions for dissolution of benzoin (3) in all the {ethyl acetate (1)+ethanol (2)} cosolvent mixtures including those for the pure solvents and the ideal solution processes.

The standard Gibbs energy of dissolution is positive in all cases as also is the enthalpy of dissolution; therefore, the process is always endothermic. The decreased enthalpy between pure ethanol and the mixture with $w_1^{\circ} = 0.90$, indicates that solubility is favored by dissolution entropy in these mixtures. Finally, between the mixture $w_1^{\circ} = 0.90$ and the pure ethyl acetate, the enthalpy increases.

Regarding the entropy of dissolution, it is positive in all cases which in general terms favors the benzoin solution processes. The relative contributions by

enthalpy (ζ_H) and entropy (ζ_{TS}) toward the solution processes are given by Eq. 6 and 7 (Serrezuela *et al.*, 2017a, b):

$$\zeta_H = \frac{|\Delta_{soln}H^{\circ}|}{|\Delta_{soln}H^{\circ}| + |T\Delta_{soln}S^{\circ}|} \quad (6)$$

$$\zeta_{TS} = \frac{|\Delta_{soln}S^{\circ}|}{|\Delta_{soln}H^{\circ}| + |T\Delta_{soln}S^{\circ}|} \quad (7)$$

The main contributor to the (positive) standard molar Gibbs energy of solution of benzoin, in all cases is the (positive) enthalpy ($\zeta_H > 0.60$). In order to analyze the thermodynamics of benzoin dissolution processes, the diagram method applied by Perlovich in the previous works is used (Perlovich *et al.*, 2008). The experimental data of the dissolution functions of this compound are collected in Fig. 4. The regions of triangular sector I Fig. 4 correspond to enthalpy determined processes [sector I ($\Delta_{soln}H^{\circ} > T\Delta_{soln}S^{\circ} > 0$)]. The graphical analysis agrees with the results of Eq. 6 and 7.

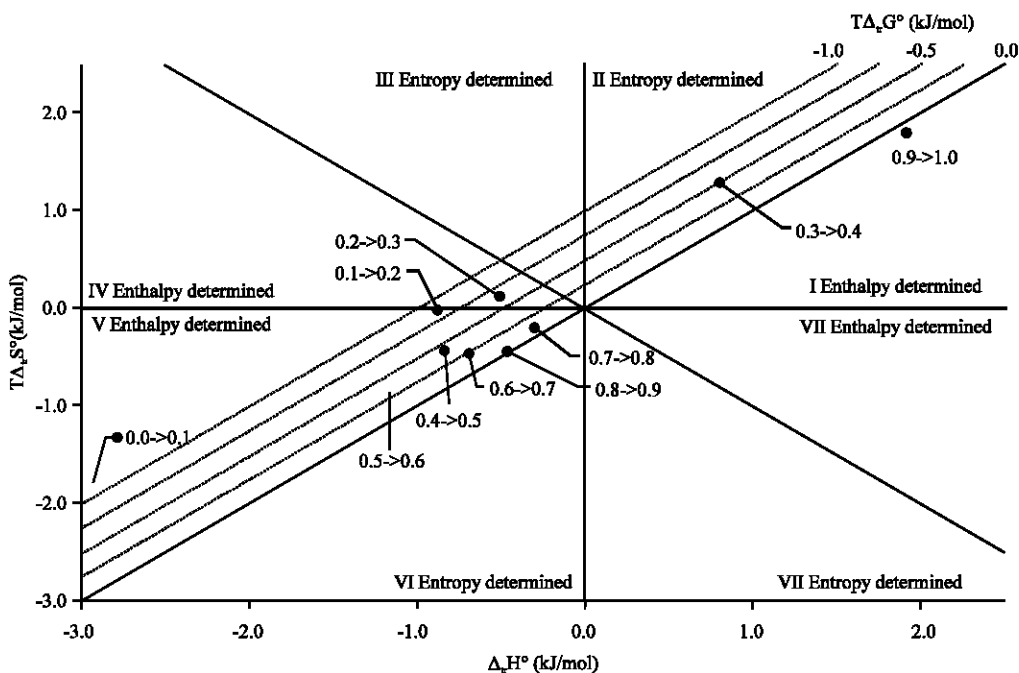


Fig. 5: Relationship between the enthalpy and entropic terms of transfer functions of benzoin from more polar solvents to less polar solvents at $T_{hm} = 303.0$ K. The isoenergetic curves of $\Delta_{tr}G^\circ$ function are marked by dotted lines

Thermodynamic functions of benzoin transfer: In order to verify the effect of cosolvent composition on the thermodynamic function driving the dissolution process, Fig. 5 collected the thermodynamic functions of transfer of benzoin (3) from the more polar solvents to the less polar ones. These new functions were calculated as the differences between the thermodynamic quantities of dissolution obtained in the less polar mixtures and the more polar ones by means of:

$$\Delta_{tr}F^\circ = \Delta_{soln}F^\circ_{less\ polar} - \Delta_{soln}F^\circ_{more\ polar} \quad (8)$$

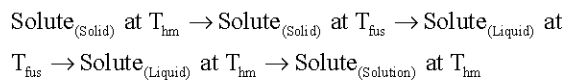
where, $\Delta_{soln}F^\circ$ thermodynamic functions ($\Delta_{soln}G^\circ$, $\Delta_{soln}H^\circ$ or $\Delta_{soln}S^\circ$). This procedure is the same followed previously with other studies (Trujillo *et al.*, 2017; Delgado *et al.*, 2011).

So, if the addition of ethyl acetate to neat ethanol is considered (being the cosolvent mixture less polar as the ethyl acetate proportion increases), it happens the following: from pure ethanol up to 0.1 in mass fraction of ethyl acetate ($[(\Delta_{tr}H^\circ < 0; T_{\Delta tr}S^\circ < 0; |\Delta_{tr}H^\circ| > |T_{\Delta tr}S^\circ|) = \text{Sector V}]$) the dissolution process is determined by the enthalpy, from this composition up to 0.30 in mass fraction of ethyl acetate ($[(T_{\Delta tr}S^\circ > \Delta_{tr}H^\circ < 0) = \text{Sector IV}]$) the dissolution process is determined by enthalpy, again and enthalpy and entropy favouring. From the mixture with $w_1^\circ = 0.30$ up to $w_1^\circ = 0.40$ ($[(T_{\Delta tr}S^\circ > \Delta_{tr}H^\circ > 0) = \text{Sector II}]$) the dissolution processes is determined by entropy. From

this composition up to $w_1^\circ = 0.9$ ($[(\Delta_{tr}H^\circ < 0; T_{\Delta tr}S^\circ < 0; |\Delta_{tr}H^\circ| > |T_{\Delta tr}S^\circ|) = \text{Sector V}]$) the processes is determined by the enthalpy. Ultimately, from 0.90 in mass fraction of ethyl acetate up to neat ethyl acetate ($[(\Delta_{tr}H^\circ > T_{\Delta tr}S^\circ > 0) = \text{Sector I}]$) the dissolution process is enthalpy-driven. It is important to clarify that the transfer process from $w_1^\circ = 0.95$ up to pure ethyl acetate, $\Delta_{tr}G^\circ$ is positive, indicating that the hypothetical transfer of benzoin to a medium of lower polarity (as the mixture with $w_1^\circ = 0.95$) will not occur where enthalpy is the main factor involved.

Apparent thermodynamic quantities of benzoin mixing:

The overall dissolution process may be represented by the following hypothetic stages (Delgado *et al.*, 2016):



where, the hypothetical dissolution stages are the heating and fusion of the drug, the cooling of the liquid drug to the considered Temperature ($T_{hm} = 302.6$ K) and then the subsequent mixing of the hypothetical super-cooled liquid drug with the solvent mixture at this temperature (Delgado *et al.*, 2016). As has been already described, this treatment also allows the calculation of the apparent partial thermodynamic contributions to the overall dissolution process by means of the following equations:

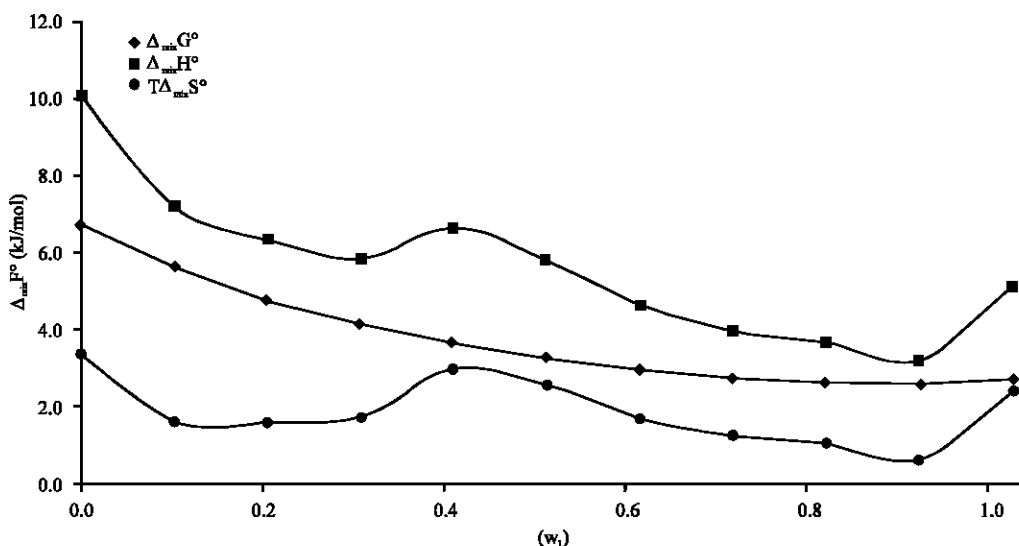


Fig. 6: Apparent thermodynamic quantities of mixing of benzoin (3) in {ethyl acetate (1)+ethanol (2)} mixtures at $T_m = 303.0$ K as function of co-solvent mixtures composition

$$\Delta_{\text{soln}} F^\circ = \Delta_{\text{fis}} F^{303} + \Delta_{\text{mix}} F^\circ \quad (9)$$

where, F are the thermodynamic functions (G, H, S). As it has been described previously in the literature, in this research the $\Delta_{\text{mix}} F^{\text{id}}$ values for the ideal solution processes were used instead of $\Delta_{\text{fis}} F^{303}$. Figure 6 depicts the apparent thermodynamic quantities of mixing of the super-cooled liquid benzoin (3) with all the {ethyl acetate (1)+ethanol (2)} cosolvent mixtures.

Gibbs energy of mixing is positive in all cases and decreases from pure ethanol up to $w_1^\circ = 0.90$, later, it presents an increase to pure ethyl acetate. Moreover, the enthalpy of mixing decreases from pure ethanol up to $w_1^\circ = 0.30$, then, from this mixture up to $w_1^\circ = 0.40$ it increases and from this mixture up to $w_1^\circ = 0.90$ it decreases again. Subsequently, from $w_1^\circ = 0.90$ up to pure ethyl acetate, it increases again. Regarding the mixing entropy, this property presents a behavior analogous to that of mixing enthalpy. These variations are a consequence of the different solute-solute, solvent-solvent and solute-solvent interactions that occur in the hypothetical process of mixing of the liquids, that is the binary {ethyl acetate (1)+ethanol (2)} solvent mixture and the supercooled liquid solute.

The enthalpy of formation of the cavity between the solvent molecules to contain the solute molecule is positive, since, it is necessary to supply energy to break the cohesive forces between the solvent molecules, so, this process is not favorable for the solubility of benzoin. In this context, the enthalpy decreasing presented in the $0.0 = w_1^\circ = 0.90$ region could be a consequence of the

increase in solute-solvent interactions (e_{13}) which is an exothermic process favorable to the dissolution process. It is a result of the van der Waals and Lewis acid-base interactions. The reduction of the energy necessary for the formation of the cavity as the proportion of ethyl acetate increases in the $0.00 = w_1^\circ = 0.90$ region. From this mixture up to pure ethyl acetate, $\Delta_{\text{mix}} H^\circ$ and $\Delta_{\text{mix}} S^\circ$ present an increase which is possibly due to the increase of solute-solvent interactions, increasing the solvation of benzoin by ethyl acetate possibly by the generation of an environment with a similar polarity to that of benzoin (Delgado *et al.*, 2011). Finally, $T\Delta_{\text{mix}} S^\circ$ is positive in all cases, contrasting with the low solder-ability of benzoin in rich mixtures in ethanol, in mixtures rich in ethyl acetate there is an increase in this thermodynamic function, concordant with the increase in the solubility of benzoin

Enthalpy–entropy compensation analysis of benzoin:

According to the literature, the making of weighted graphs of $\Delta_{\text{soln}} H^\circ$ as a function of $\Delta_{\text{soln}} G^\circ$ at mean harmonic temperature allows us to observe similar mechanisms for the dissolution process according to the tendencies obtained (Ramos *et al.*, 2018; Martinez *et al.*, 2011). A second relevant kind of compensation plot is that one obtained by plotting of $\Delta_{\text{soln}} H^\circ$ as a function of $T\Delta_{\text{soln}} S^\circ$. In this context, Fig. 7 shows fully that benzoin in the {ethyl acetate (1)+ethanol (2)} cosolvent system present nonlinear $\Delta_{\text{soln}} H^\circ$ vs. $\Delta_{\text{soln}} G^\circ$ compensation with positive slope if an interval from pure ethyl acetate up to $w_1^\circ = 0.90$ and from $w_1^\circ = 0.40$ up to $w_1^\circ = 0.30$. On the other hand, from pure ethanol up to $w_1^\circ = 0.03$ and from $w_1^\circ = 0.34$ up

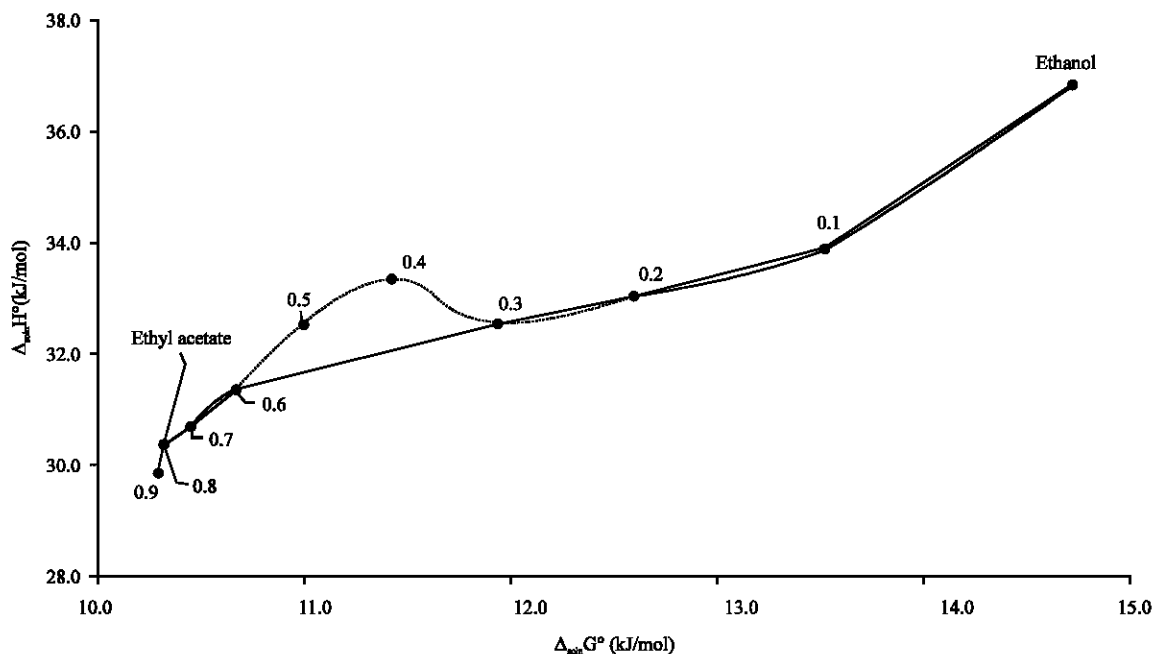


Fig. 7: $\Delta_{\text{soln}}H^\circ$ vs. $\Delta_{\text{soln}}G^\circ$ enthalpy-entropy compensation plot for dissolution process of benzoin in {ethyl acetate (1)+ethanol (2)} mixtures at $T_{\text{fm}} = 302.6$ K

to $w_1^\circ = 0.05$ a negative slope is obtained. Accordingly, it follows that the driving function for the drug dissolution process is the enthalpy in the former case while in the second case, the driving function is mainly the entropy (Gantiva and Martinez, 2010).

CONCLUSION

The equilibrium solubility of benzoin in {ethyl acetate (1)+ethanol (2)} mixtures at 283.15-323.15 K was reported. Mole fraction solubility of benzoin increases continuously from neat ethanol to neat ethyl acetate at all temperatures studied. Based on the Gibbs and van't Hoff equations the respective apparent thermodynamic quantities of dissolution of benzoin were calculated in all the mixtures and neat solvents. Non-linear enthalpy-entropy compensation analysis is observed indicating different dissolution mechanism of benzoin with the variation in the ethyl acetate proportion of the cosolvent.

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REFERENCES

- Benavides, L.C.L., L.A.C. Pinilla, J.S.G. Lopez and R.R. Serrezuela, 2018. Electrogenic biodegradation study of the carbofuran insecticide in soil. *Intl. J. Appl. Eng. Res.*, 13: 1776-1783.
- Cardenas, Z.J., D.M. Jimenez and F. Martinez, 2015. Solubility and solution thermodynamics of meloxicam in polyethylene glycol 400+ water mixtures. *J. Mol. Liq.*, 211: 233-238.
- Cardenas, Z.J., D.M. Jimenez, D.R. Delgado, O.A. Almanza and A. Jouyban *et al.*, 2017. Solubility and preferential solvation of some N-alkyl-parabens in methanol+water mixtures at 298.15 K. *J. Chem. Thermodyn.*, 108: 26-37.
- Carl, G.F. and M.L. Smith, 1992. Phenytoin-folate interactions: Differing effects of the sodium salt and the free acid of phenytoin. *Epilepsia*, 33: 372-375.
- Carvajal, R.J.H., R.R. Serrezuela, J.A.Q. Lopez and K.L.R. Perdomo, 2016. LQR hybrid approach control of a robotic arm two degrees of freedom. *Intl. J. Appl. Eng. Res.*, 11: 9221-9228.

- Connors, K.A., 2002. Thermodynamics of Pharmaceutical Systems: An Introduction for Students of Pharmacy. Wiley, Hoboken, New Jersey, USA., ISBN:9780471202417, Pages: 344.
- Cristancho, D.M., A. Jouyban and F. Martinez, 2016. Solubility, solution thermodynamics and preferential solvation of piroxicam in ethyl acetate+ ethanol mixtures. *J. Mol. Liq.*, 221: 72-81.
- Delgado, D.R., A.R. Holguin and F. Martinez, 2012. Solution thermodynamics of triclosan and triclocarban in some volatile organic solvents. *Vitae*, 19: 79-92.
- Delgado, D.R., A.R. Holguin, O.A. Almanza, F. Martinez and Y. Marcus, 2011. Solubility and preferential solvation of meloxicam in ethanol+ water mixtures. *Fluid Phase Equilib.*, 305: 88-95.
- Delgado, D.R., O.A. Almanza, F. Martinez, M.A. Pena and A. Jouyban *et al.*, 2016. Solution thermodynamics and preferential solvation of sulfamethazine in (methanol+ water) mixtures. *J. Chem. Thermodyn.*, 97: 264-276.
- Gantiva, M. and F. Martinez, 2010. Thermodynamic analysis of the solubility of ketoprofen in some propylene glycol+ water cosolvent mixtures. *Fluid Phase Equilib.*, 293: 242-250.
- Jouyban, A., 2009. Handbook of Solubility Data for Pharmaceuticals. CRC Press, Boca Raton, Florida, USA., ISBN:9781439804889, Pages: 552.
- Kristl, A. and G. Vesnaver, 1995. Thermodynamic investigation of the effect of octanol-water mutual miscibility on the partitioning and solubility of some guanine derivatives. *J. Chem. Soc. Faraday Trans.*, 91: 995-998.
- Krug, R.R., W.G. Hunter and R.A. Grieger, 1976. Enthalpy-entropy compensation: 2. Separation of the chemical from the statistical effect. *J. Phys. Chem.*, 80: 2341-2351.
- Letcher, T.M., 2007. Thermodynamics, Solubility and Environmental Issues. Elsevier, Amsterdam, Netherlands, ISBN:9780080481036, Pages: 492.
- Losada, V.A.R., E.P. Bonilla, L.A.C. Pinilla and R.R. Serrezuela, 2018. Removal of chromium in wastewater from tanneries applying bioremediation with algae, orange peels and citrus pectin. *Contemp. Eng. Sci.*, 11: 433-449.
- Mahmoodi, N.O. and S. Emadi, 2004. One-pot synthesis of phenytoin analogs. *Russ. J. Org. Chem.*, 40: 377-382.
- Martinez, F., M.A. Pena and P. Bustamante, 2011. Thermodynamic analysis and enthalpy-entropy compensation for the solubility of indomethacin in aqueous and non-aqueous mixtures. *Fluid Phase Equilib.*, 308: 98-106.
- Montiel, J.J.G., R.R. Serrezuela and E.A. Aranda, 2017. Applied mathematics and demonstrations to the theory of optimal filters. *Global J. Pure Appl. Mathe.*, 13: 475-492.
- Pedraza, N.A.P., J.I.P. Montealegre and R.R. Serrezuela, 2018. Feasibility analysis for creating a metrology laboratory serving the Agribusiness and Hydrocarbons in the Department of Huila, Colombia. *Intl. J. Appl. Eng. Res.*, 13: 3373-3378.
- Pena, M.A., B. Escalera, A. Reillo, A.B. Sanchez and P. Bustamante, 2009. Thermodynamics of cosolvent action: Phenacetin, salicylic acid and probenecid. *J. Pharm. Sci.*, 98: 1129-1135.
- Perdomo, E.G., M.A.T. Cardozo, C.C. Perdomo and R.R. Serrezuela, 2017. A review of the user based web design: Usability and information architecture. *Intl. J. Appl. Eng. Res.*, 12: 11685-11690.
- Perlovich, G.L., N.N. Strakhova, V.P. Kazachenko, T.V. Volkova and V.V. Tkachev *et al.*, 2008. Sulfonamides as a subject to study molecular interactions in crystals and solutions: Sublimation, solubility, solvation, distribution and crystal structure. *Intl. J. Pharm.*, 349: 300-313.
- Ramos, A.M.N., J.L.A. Trujillo, R.R. Serrezuela and J.B.R. Zarta, 2018. A Review of the Hotel Sector in the City of Neiva and the Improvement of its Competitiveness through Quality Management Systems. In: *Advanced Engineering Research and Applications*, Ajaykumar, B.S. and D. Sarkar (Eds.). Research India Publication, Nueva Deli, India, pp: 439-452.
- Ruidiaz, M.A., D.R. Delgado, F. Martinez and Y. Marcus, 2010. Solubility and preferential solvation of indomethacin in 1, 4-dioxane+ water solvent mixtures. *Fluid Phase Equilibria*, 299: 259-265.
- Sanchez, N.C., A.L.P. Salazar, A.M.N. Ramos, Y.M. Calderon and R.R. Serrezuela, 2018. Optimization of the Paddy rice husking process, increasing the useful life of the rollers in Florhuila plant Campoalegre mills. *Intl. J. Appl. Eng. Res.*, 13: 3343-3349.
- Serrezuela, R.R. and A.F.C. Chavarro, 2016. Multivariable control alternatives for the prototype tower distillation and evaporation plant. *Intl. J. Appl. Eng. Res.*, 11: 6039-6043.
- Serrezuela, R.R., A.F. Chavarro, M.A.T. Cardozo, A.G. Rey and C.A. Cabrera, 2017a. Audio signals processing with digital filters implementation using MyDSP. *J. Eng. Appl. Sci.*, 12: 5-10.
- Serrezuela, R.R., A.F.C. Chavarro, M.A.T. Cardozo and J.B.R. Zarta, 2016a. An optimal control based approach to dynamics autonomous vehicle. *Intl. J. Appl. Eng. Res.*, 11: 8841-8847.

- Serrezuela, R.R., A.F.C. Chavarro, M.A.T. Cardozo, A.L. Toquica and L.F.O. Martinez, 2017b. Kinematic modelling of a robotic arm manipulator using MATLAB. *J. Eng. Appl. Sci.*, 12: 2037-2045.
- Serrezuela, R.R., J.A. Trujillo, A.N. Ramos and J.R. Zarta, 2018a. Applications Alternatives of Multivariable Control in the Tower Distillation and Evaporation Plant. In: *Advanced Engineering Research and Applications*, Ajaykumar, B.S. and D. Sarkar (Eds.). Research India Publication, Delhi, India, pp: 452-465.
- Serrezuela, R.R., M.A.T. Cardozo, D.L. Ardila and C.A.C. Perdomo, 2017c. Design of a gas sensor based on the concept of digital interconnection IoT for the emergency broadcast system. *J. Eng. Appl. Sci.*, 12: 6352-6356.
- Serrezuela, R.R., M.A.T. Cardozo, D.L. Ardila and C.A.C. Perdomo, 2018b. A consistent methodology for the development of inverse and direct kinematics of robust industrial robots. *ARN. J. Eng. Appl. Sci.*, 13: 293-301.
- Serrezuela, R.R., O.F. Villar, J.R. Zarta and Y.H. Cuenca, 2016b. The k-exponential matrix to solve systems of differential equations deformed. *Global J. Pure Appl. Math.*, 12: 1921-1945.
- Trujillo, J.A., R.R. Serrezuela, J.R. Zarta and A.N. Ramos, 2018. Direct and Inverse Kinematics of a Manipulator Robot of Five Degrees of Freedom Implemented in Embedded System-CompactRIO. In: *Advanced Engineering Research and Applications*, Ajaykumar, B.S. and D. Sarkar (Eds.). Research India Publication, Delhi, India, pp: 405-419.
- Trujillo, J.L.A., A. Perez-Ruiz and R. Rodriguez Serrezuela, 2017. Generation and control of basic geometric trajectories for a robot manipulator using compact RIO®. *J. Rob.*, 2017: 1-11.
- Ueyama, N., N. Yoshinaga, T.A. Okamura, H. Zaima and A. Nakamura, 1991. O-atom transfer biomimetic oxidation of benzoin in the presence of monooxomolybdenum (IV) thiolate complexes. *J. Mol. Catal.*, 64: 247-256.
- Yang, Y., W. Tang, S. Liu, D. Han and Y. Liu *et al.*, 2017a. Solubility of benzoin in three binary solvent mixtures and investigation of intermolecular interactions by molecular dynamic simulation. *J. Mol. Liq.*, 243: 472-483.
- Yang, Y., W. Tang, X. Li, D. Han and Y. Liu *et al.*, 2017b. Solubility of benzoin in Six Monosolvents and in some binary solvent mixtures at Various Temperatures. *J. Chem. Eng. Data*, 62: 3071-3083.